

## 6.04 CABOZANTINIB, Tablet 20 mg, 40 mg, 60 mg, Cabometyx<sup>®</sup>, Ipsen Pty Ltd

### 1 Purpose of submission

- 1.1 The Category 2 submission requested an amendment to the existing General Schedule Authority Required (STREAMLINED) listing for cabozantinib to remove the ‘clear cell variant’ histology requirement to allow treatment in patients with non-clear cell renal cell carcinoma (nccRCC).
- 1.2 Listing was requested on the basis of a ‘frame of reference’ comparison between cabozantinib versus sunitinib in the ccRCC setting, and cabozantinib versus sunitinib in the nccRCC setting.
- 1.3 Table 1 presents the key components of the clinical issue addressed by the submission.

**Table 1: Key components of the clinical issue addressed by the submission**

Component	Description
Population	Patients with treatment-naïve (Stage IV) nccRCC who are classified as intermediate or poor risk according to the IMDC prognostic criteria and patients with Stage IV nccRCC who have received prior treatment with a TKI.
Intervention	Cabozantinib 60mg orally once daily
Comparator	Sunitinib 50mg orally once daily
Outcomes	PFS, ORR, OS, and safety
Clinical claim	In adults with Stage IV nccRCC, ECOG status of 0-2, with intermediate to poor risk disease according to IMDC criteria, compared to sunitinib, cabozantinib has: <ul style="list-style-type: none"> <li>• Significantly superior PFS and ORR;</li> <li>• Similar OS and</li> <li>• Different but broadly comparable safety.</li> </ul> The submission also claimed that the relative effectiveness of cabozantinib over sunitinib in PFS and ORR observed in nccRCC is similar to that observed in ccRCC.

Source: Table 1.1, p12 of the submission.

ECOG = Eastern Cooperative Oncology Group, IMDC = International Metastatic Database Consortium, ORR = objective response rate, OS = overall survival, PFS = progression free survival, ccRCC = clear cell renal cell carcinoma, nccRCC = non-clear cell renal cell carcinoma, TKI = tyrosine kinase inhibitor.

### 2 Background

#### **Registration status**

- 2.1 Cabozantinib was TGA registered on 31 October 2018 for the following indication: as monotherapy for the treatment of advanced renal cell carcinoma (aRCC) in treatment-naïve adults with intermediate or poor risk and in adults following prior treatment with vascular endothelial growth factor (VEGF) targeted therapy.
- 2.2 Cabozantinib is also indicated, in combination with nivolumab, for the first-line treatment of aRCC.

### Previous PBAC consideration

- 2.3 Cabozantinib is currently PBS listed for patients with clear cell aRCC as monotherapy in the first-line treatment setting (intermediate or poor International Metastatic Database Consortium (IMDC) risk only) and for patients following tyrosine kinase inhibitor (TKI) treatment (regardless of IMDC risk score).
- 2.4 Cabozantinib in combination with nivolumab for the first-line treatment of clear cell aRCC will be considered at the March 2024 PBAC meeting.

For more detail on PBAC’s view, see section 7 PBAC outcome.

### 3 Requested listing

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	No.of Rpts	Available brands
CABOZANTINIB					
Cabozantinib 20 mg tablet, 30	\$9,962.13 published price \$█ effective price	1	30	2 (initial) 5 (continuing) 5 (grandfather)	Cabometyx
Cabozantinib 40 mg tablet, 30		1	30		
Cabozantinib 60 mg tablet, 30		1	30		
<b>Category / Program:</b> General Schedule/Section 85					
<b>Prescriber type:</b> <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/>					
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (STREAMLINED)					
<b>Indication:</b> Stage IV renal cell carcinoma (RCC)					
<b>Treatment Phase:</b> Initial treatment					
<b>Clinical criteria:</b>					
The condition must be each of: (i) classified as having an intermediate to poor survival risk score according to the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC), (ii) untreated with a tyrosine kinase inhibitor					
<b>OR</b>					
<b>Clinical criteria:</b>					
Patient must have progressive disease according to the Response Evaluation Criteria in Solid Tumours (RECIST) despite treatment with a tyrosine kinase inhibitor, irrespective of the current IMDC survival risk score					
<b>AND</b>					
<b>Clinical criteria:</b>					
Patient must have a WHO performance status of 2 or less					
<b>AND</b>					
<b>Clinical criteria:</b>					
The treatment must be the sole PBS-subsidised therapy for this condition.					
<b>Treatment criteria:</b>					
Patient must be undergoing treatment with this drug for the first time at the time of the first PBS prescription.					
<b>Treatment Phase:</b> Continuing treatment					
<b>Clinical criteria:</b>					
Patient must have stable or responding disease according to the Response Evaluation Criteria In Solid Tumours (RECIST)					
<b>AND</b>					
<b>Clinical criteria:</b>					
The treatment must be the sole PBS-subsidised therapy for this condition.					
<b>AND</b>					

<b>Clinical criteria:</b>
Patient must not receive PBS-subsidised treatment with this drug if progressive disease develops while on this drug.
<b>Treatment criteria:</b>
Patient must have previously received PBS-subsidised treatment with this drug for this condition
<b>Treatment Phase:</b> Transitioning from non-PBS to PBS-subsidised supply - Grandfather arrangements for maintenance treatment
<b>Clinical criteria:</b>
Patient must have had a prognostic International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) survival risk classification score at treatment initiation with this of either: (i) 1 to 2 (intermediate risk), (ii) 3 to 6 (poor risk); document the IMDC risk classification score in the patient's medical records if not already documented,
<b>AND</b>
<b>Clinical criteria:</b>
Patient must have stable or responding disease according to the Response Evaluation Criteria In Solid Tumours (RECIST)
<b>AND</b>
<b>Clinical criteria:</b>
The treatment must be the sole PBS-subsidised therapy for this condition.
<b>AND</b>
<b>Clinical criteria:</b>
Patient must not receive PBS-subsidised treatment with this drug if progressive disease develops while on this drug.
<b>Treatment criteria:</b>
Patient must have previously received non-PBS-subsidised treatment with this drug for this condition.
<b>Notes:</b> Patients may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a 'Grandfathered' patient must qualify under the 'Maintenance treatment' criteria. This grandfather restriction will cease to operate from 12 months after listing

Source: Table 1-10, p34, Table 1-11, p35, Table 1-12, p36 of submission.

IMDC = International Metastatic Renal Cell Carcinoma Database Consortium, PBS = Pharmaceutical Benefits Scheme, RCC = renal cell carcinoma, RECIST = Response Evaluation Criteria in Solid Tumours, WHO = World Health Organization.

- 3.1 The submission requested to remove 'clear cell variants' from the current PBS listing indication to broaden the listing and cover all RCC subtypes. However, SWOG 1500 (the key clinical trial) only included patients with papillary RCC and there is limited clinical data available in other nccRCC subtypes. The PBAC considered that the proposed change to the indication was reasonable, and considered that it was preferable to maintain the same circumstances of use across all advanced RCC.
- 3.2 In SWOG 1500, only 7% of total patients and 5% of patients who received cabozantinib had previous systemic therapy. SWOG 1500 also included patients with favourable IMDC risk (26% of total patients and 23% in cabozantinib arm). As there are currently no TKIs PBS listed for nccRCC it would be expected that the majority of PBS patients would be treated in the first line setting. The Pre-Sub-Committee Response (PSCR) stated that access in the second line setting is essential for patients who have accessed previous systemic therapy through a clinical trial or access program. The ESC agreed with the Commentary that, if PBS listed, nccRCC patients would be treated with cabozantinib almost exclusively as first line treatment as there are no PBS-listed alternatives. The PBAC considered that cabozantinib would be the preferred first line therapy for patients with nccRCC but considered that it would be reasonable for the

listing to include patients whose disease has progressed despite treatment with a prior TKI, consistent with the existing listing for nccRCC.

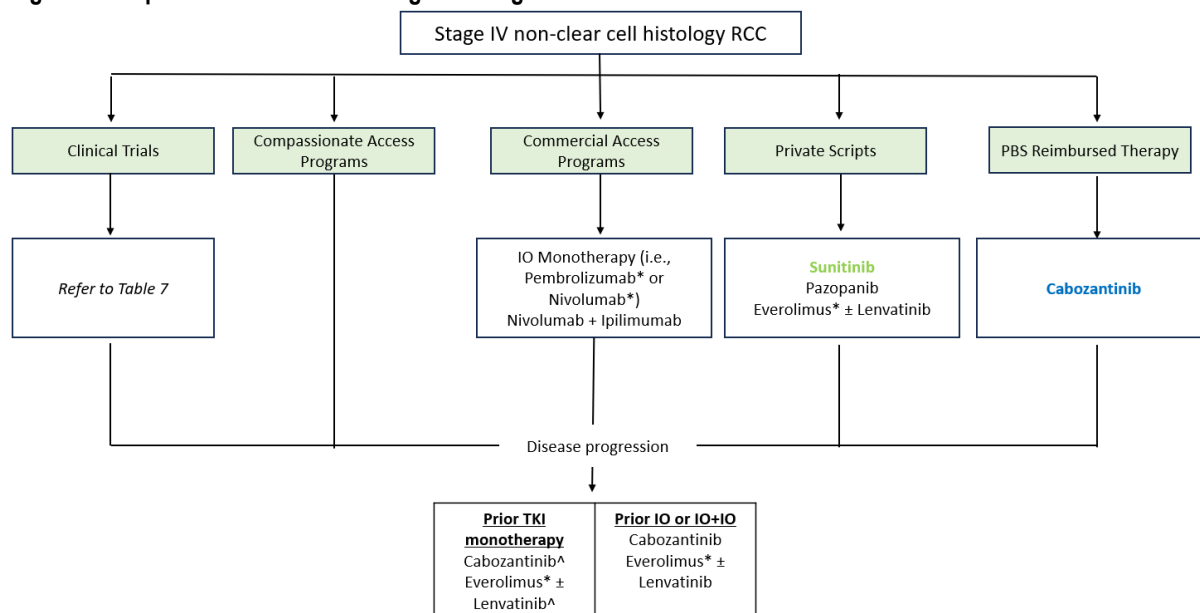
- 3.3 The submission proposed that pricing of cabozantinib in nccRCC be equal to the weighted price of cabozantinib for ccRCC, with flat pricing across all doses (i.e., 60 mg, 40 mg, and 20 mg). The proposed effective approved ex-manufacturer price (AEMP) for all doses of cabozantinib was \$1. The ESC noted the proposed weighted price was higher than the price for first line treatment of ccRCC. However, the ESC considered that the first-line price would be more applicable for this population.

*For more detail on PBAC's view, see section 7 PBAC outcome.*

## **4 Population and disease**

- 4.1 In 2022, kidney cancer was the seventh most-diagnosed cancer in Australia with 4,552 new cases (3,081 males and 1,471 females) and 912 deaths. The incidence rate for kidney cancer increases with age and is highest in individuals aged 70 to 74 years old. Approximately 85-90% of kidney cancers are RCC. Approximately 20-25% of all RCCs are nccRCC, a diverse group of tumours with distinct histological and molecular features. The subtypes of nccRCC include papillary RCC (10-15% of all RCC subtypes, approximately half of nccRCC), chromophobe RCC, collecting duct RCC, Microphthalmia Transcription Factor (MiT) family translocation RCC, malignant potential, and others.
- 4.2 Figure 1 illustrates the proposed local clinical management algorithm for metastatic nccRCC.

Figure 1: Proposed local clinical management algorithm for metastatic nccRCC#



Source: Figure 1-5, p20 of the submission.

RCC=Renal cell carcinoma. \*Single agent nivolumab or pembrolizumab, and everolimus (monotherapy and in combination with lenvatinib) are not TGA-registered to be used in the first line setting for advanced RCC.

# Cabozantinib recommendation on PBS is for use in poor and intermediate risk patients as per proposed restrictions below

^ Only if cabozantinib has not been use in the first-line setting.

Note: Green text indicates the primary comparator.

4.3 The proposed intervention is cabozantinib, a small molecule that inhibits multiple receptor tyrosine kinases (RTKs), including the mesenchymal-epithelial transition (MET) protein, anexelekto (AXL), and vascular endothelial growth factor (VEGF) receptors. RTKs play critical roles in tumour growth, angiogenesis, bone remodelling, drug resistance, and metastatic progression.

4.4 The recommended dose of cabozantinib is 60 mg orally once daily until disease progression or unacceptable toxicity is observed. Lower doses of cabozantinib (40 mg and 20 mg) were proposed for the management of toxicity and adverse events.

*For more detail on PBAC’s view, see section 7 PBAC outcome.*

## 5 Comparator

5.1 Currently, there are no medicines PBS-listed for use in nccRCC that can be used as comparators. Sunitinib was nominated as the primary comparator because it is among the treatment options for nccRCC patients recommended by the National Comprehensive Cancer Network (NCCN) clinical practice guidelines (version 1.2024).

5.2 The submission did not consider other potential comparators. The NCCN Clinical Practice Guidelines (version 1.2024) recommend cabozantinib and clinical trials as a "Preferred Regimen" and list sunitinib, lenvatinib + everolimus, nivolumab, and cabozantinib + nivolumab as "other recommended regimens" for nccRCC. The ESC noted that clinical trials are not a practical option for many patients with nccRCC.

- 5.3 Although not PBS-subsidised for nccRCC, other drugs that are PBS listed in advanced ccRCC could be considered potential comparators, including immunotherapy such as nivolumab monotherapy and combinations including nivolumab + ipilimumab and pembrolizumab + lenvatinib. The ESC agreed with the PSCR that there is very little evidence for immunotherapies in patients with nccRCC and considered that sunitinib was the most reasonable comparator for the ‘frame of reference’ approach presented.

*For more detail on PBAC’s view, see section 7 PBAC outcome.*

## **6 Consideration of the evidence**

### ***Sponsor hearing***

- 6.1 The sponsor requested a hearing for this item. The clinician presented a clinical perspective on treatment needs for nccRCC. The clinician noted that patients with ccRCC have several treatment options, however for the small number of patients with nccRCC, there are no targeted treatments available on the PBS, only the Ipsen cabozantinib access program and clinical trials. The clinician noted that patients with nccRCC can often be relatively young and well and it is important for second line treatment to be available for those who have previously received first line treatment through clinical trials.
- 6.2 The clinician noted that based on clinical experience with cabozantinib, it is clearly active in patients with nccRCC and there is no obvious distinction in how patients with different subtypes respond to treatment. In addition, though some clinical trial data suggests that there is a lower response rate for patients with chromophobe subtypes, the disease control rate appears similar and the treatment benefit may be less clear within the trial duration because disease tends to be more indolent for this subtype.

### ***Consumer comments***

- 6.3 The PBAC noted and welcomed the input from health care professionals (8) and organisations (3) via the Consumer Comments facility on the PBS website. The comments acknowledged that not all individuals with nccRCC will respond to cabozantinib but stated that there is increasing evidence that it is active in nccRCC, particularly papillary and chromophobe sub-types. Health care professionals with clinical experience treating patients with nccRCC reported that it was an effective therapy in improving quality of life, cancer-related symptoms, and survival outcomes. Comments noted that cabozantinib has a well-studied range of side effects that are managed commonly by oncologists who use the medicine to treat patients with ccRCC. Health care providers also noted the major unmet clinical need for access to systemic therapies to treat nccRCC as there are no PBS-funded treatments for this group and the cost to privately fund treatment is prohibitive. The comments noted that compassionate access programs and access to trials are not guaranteed, not available to all patients, and many patients progress while awaiting approval.

- 6.4 The PBAC noted the advice received from ANZUP Cancer Trials Group, which referenced the UNICAB trial conducted by ANZUP. In this trial patients with nccRCC, refractory or intolerant to immunotherapy, were treated with cabozantinib. The comments noted that cabozantinib is clearly active in some nccRCC and can lead to prolonged responses. The PBAC also noted advice from Rare Cancers Australia (RCA) regarding the cabozantinib submission. Comments from RCA noted that patients felt there was inequity in excluding nccRCC from the current listings for treatments in ccRCC and noted that cabozantinib was included in the treatment guidelines for nccRCC and is included as the preferred treatment for nccRCC in similar jurisdictions including the UK and Canada. Both the ANZUP and RCA highlighted the unmet clinical need for access to active therapies for nccRCC.
- 6.5 The Medical Oncology Group of Australia (MOGA) also expressed its strong support for the cabozantinib submission, categorising it as one of the therapies of “high priority for PBS listing”. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for cabozantinib in nccRCC, which was limited to 3 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)<sup>1</sup>.

### **Clinical trials**

- 6.6 The submission was based on two head-to-head prospective randomised controlled trials (RCT) comparing cabozantinib and sunitinib for the treatment of advanced nccRCC:
- SWOG 1500 (also known as PAPMET; NCT02761057; N=152) was a Phase 2, open-label randomised trial that evaluated the efficacy, effectiveness, and safety of cabozantinib compared with sunitinib in the treatment of advanced papillary RCC. Patients were randomly assigned to the control group of sunitinib (n=46) or to one of three investigational groups: cabozantinib (n=44), crizotinib (n=28), and savolitinib (n=29). For this trial, the duration of treatment and follow-up was until death or three years after registration.
  - CABOSUN II (NCT03541902; N=32) was a phase 2, open-label, multicentre randomised trial that evaluated the effectiveness of cabozantinib (n=15) compared with sunitinib (n=17) in the treatment of advanced nccRCC. CABOSUN II was only available as an abstract and did not provide comprehensive safety outcomes. Details of the trials presented in the submission are provided in Table 2.

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<sup>1</sup> Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Annals of Oncology* 28:2340-2366, 2017]

**Table 2: Trials presented in the submission**

Trial ID	Protocol title/ Publication title	Publication citation
SWOG 1500 (NCT02761057) Also known as PAPMET	Testing Cabozantinib, Crizotinib, Savolitinib and Sunitinib in Kidney Cancer Which Has Progressed. Pal, S. K., et al. (2021). A comparison of sunitinib with cabozantinib, crizotinib, and savolitinib for treatment of advanced papillary renal cell carcinoma: a randomised, open-label, phase 2 trial.	September 16, 2021  The Lancet 397(10275): 695-703.
CABOSUN II (NCT03541902)	Cabozantinib or Sunitinib Malate in Treating Participants With Metastatic Variant Histology Renal Cell Carcinoma. Johns, A., et al. (2023). CABOSUN II: Results from a phase 2, open-label, multi-center randomized study of cabozantinib (CABO) vs. sunitinib (SUN) for non-clear cell renal cell carcinoma (NCCRCC).	May 31, 2023  Journal of Clinical Oncology 41(16_suppl): 4597-4597.

Source: Table 2-3, p31 of the submission.

6.7 The key features of the direct randomised trials are summarised in Table 3.

**Table 3: Key features of the included evidence for cabozantinib vs. sunitinib**

Trial	N	Design/ duration	Risk of bias	Patient population	IMDC risk group	Previous treatment	Outcome(s)
SWOG 1500	Sunitinib = 46; cabozantinib = 44; crizotinib = 28; savolitinib = 29	R, OL Duration of treatment and follow up until death or 3 years post randomisation <sup>a</sup>	Moderate <sup>b</sup>	patients with PRCC only	Favourable, Intermediate, and high	7%	PFS, RR, OS, AE
CABOSUN II	Cabozantinib = 15; sunitinib = 17	R, OL Median follow up of 33 months	High	patients with metastatic nccRCC (both PRCC and non PRCC)	Good, intermediate, and high	16.6%	PFS, ORR, OS, AE

Source: Table 2-5, pp34-35; Table 2-8, pp40-41; Table 2-9, pp41-42; Table 2-10, p43 of the submission.

AE = Adverse event rate; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; nccRCC = non-clear cell renal cell carcinoma; OL = open label; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PRCC = papillary renal cell carcinoma; R = randomised; RR = Response rate.

<sup>a</sup> Median follow up was not reported.

<sup>b</sup> Overall: Medium; Low (Selection, attrition, reporting biases); High (Performance, detection and other sources)

6.8 The overall risk of bias for SWOG 1500 was moderate, while the risk of bias for CABOSUN II was high in all domains, especially in reporting bias, since the only available publication from the trial was an abstract (Johns et al., 2023).

6.9 As SWOG 1500 only included patients with papillary RCC there is limited evidence for efficacy of cabozantinib for non-papillary nccRCC. The ESC noted that papillary RCC was adopted by the submission as a proxy for other subtypes, however non-papillary RCC subtypes have different disease characteristics and responses to treatments compared to papillary RCC subtypes. The ESC noted that papillary RCC represents approximately half of nccRCC subtypes. The PSCR provided a summary of studies to demonstrate evidence in other nccRCC subtypes. However the ESC noted that these studies were low grade evidence and considered that they did not provide additional confidence regarding the relative efficacy in papillary and non-papillary sub-types.

- 6.10 CABOSUN II failed to reach its target patient accrual and was terminated early due to a change in the standard of care for nccRCC as cabozantinib replaced sunitinib as a preferred treatment option in NCCN clinical guidelines.
- 6.11 There were major differences in the non-papillary RCC subtypes between the arms of CABOSUN II. More patients with chromophobe histology, an indolent subtype, received sunitinib while all patients with MiT family translocation (an aggressive subtype) received cabozantinib. The ESC considered that imbalances in the subtypes in each treatment arm are likely to have impacted on the relative outcomes, however the direction of bias is unclear.
- 6.12 SWOG 1500 included only 5% previously received systemic therapy treated patients in the cabozantinib arm and 7% of the total patients.
- 6.13 The duration of treatment for nccRCC patients was not presented in either SWOG 1500 or CABOSUN II. Furthermore, there was no evidence of post-progression treatments in nccRCC patients from the presented clinical trial, which would make the costs, duration, and intensity of post-progression treatment uncertain in nccRCC patients. The ESC noted that subsequent treatments in SWOG 1500, including cross-over, may have impacted on OS in the trial.

### Comparative effectiveness

- 6.14 The results of progression-free survival (PFS) and overall survival (OS) are shown in Table 4. Figure 2 shows the PFS Kaplan-Meier curve and Figure 3 shows the OS Kaplan-Meier curve from SWOG 1500. CABOSUN II did not present Kaplan-Meier curves.

Table 4: Results of PFS and OS across the trials

Trial	Cabozantinib		Sunitinib		Difference in median	p-value (log rank test)	Hazard ratio (95% CI)
	n/N with event (%)	median time to event (95% CI)	n/N with event (%)	median time to event (95% CI)			
<b>PFS</b>							
SWOG 1500 <sup>a</sup>	32/44 (72.7%)	9.0 (5.6, 12.4)	38/46 (82.6%)	5.6 (2.9, 6.7)	3.4	0.019	<b>0.60 (0.37, 0.97)</b>
CABOSUN II <sup>b</sup>	11/15 (73.3%)	8.2 (4.3, not reached)	9/17 (52.9%)	13.8 (11, not reached)	-5.6	0.96	NR
<b>OS</b>							
SWOG 1500 <sup>a</sup>	22/44 (50%)	20.0 (11.3, not reached)	24/46 (52.1%)	16.4 (12.8, 21.6)	3.6	NR	0.84 (0.47, 1.51)
CABOSUN II <sup>b</sup>	9/15 (60%)	28.0 (17, not reached)	7/17 (41.1%)	34.9 (28.6, not reached)	-6.9	0.67	NR

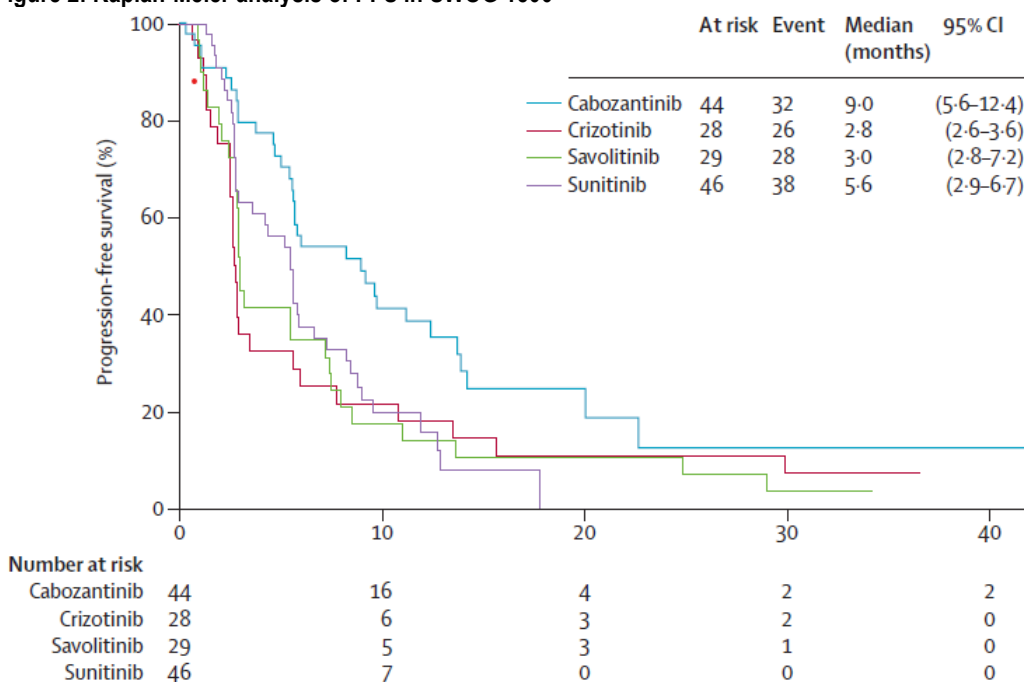
Source: Table 2-13, p47, Table 2-16, p49 of the submission; Johns et al. (2023); Pal et al. (2021).

CI = confidence interval; n = number of participants reporting data with events; N = total participants in group; OS = overall survival; PFS = progression-free survival; NR = not reported.

<sup>a</sup> Cut-off date was 16 October 2020. <sup>b</sup> study was conducted between 9/2018 and 6/2021.

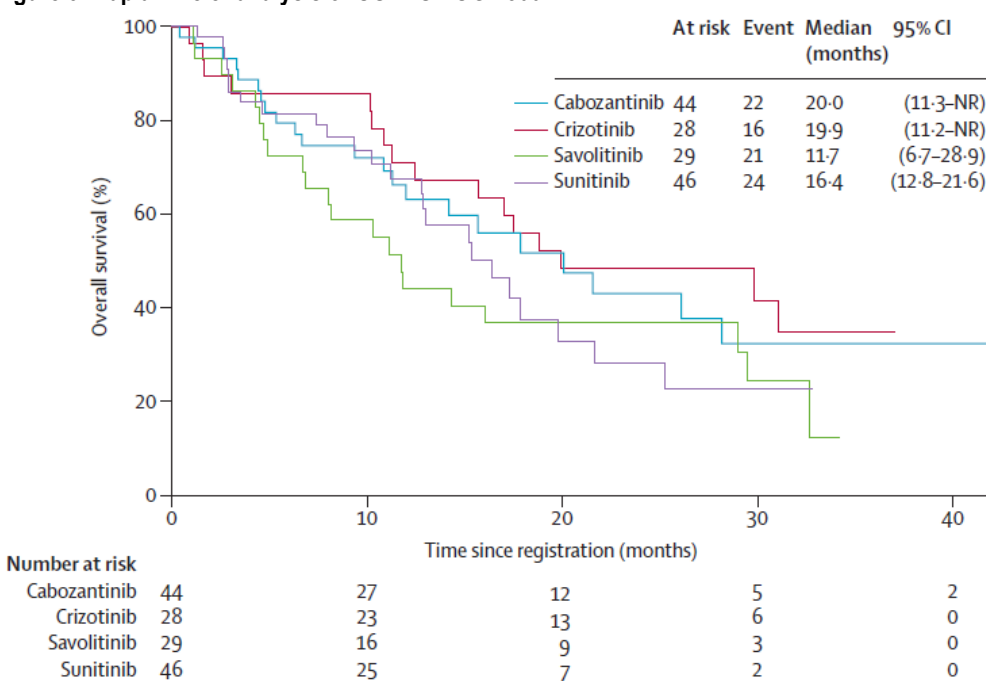
Bold indicates statistically significant results. The p-values were one-sided.

Figure 2: Kaplan-Meier analysis of PFS in SWOG 1500



Source: Figure 2-3, p48 of the submission.  
CI = confidence interval

Figure 3: Kaplan-Meier analysis of OS in SWOG 1500



Source: Figure 2-4, p50 of the submission.  
CI = confidence interval

6.15 In SWOG 1500, the median PFS was statistically significantly higher in the cabozantinib arm than in the sunitinib arm, while the results from CABOSUN II did not show a significant difference. OS was a secondary endpoint in both SWOG 1500 and CABOSUN

II, though the SWOG 1500 trial was not designed to detect differences in OS. OS was not significantly different between the cabozantinib and sunitinib arms in SWOG 1500 (3.6 months median OS benefit, HR=0.84 (95% CI: 0.47, 1.51), Table 4), though there was a trend toward improved survival as shown in Figure 3. However, results from CABOSUN II showed a lower median OS in the cabozantinib arm compared to sunitinib (-6.9 months median OS difference). The conflicting results for cabozantinib PFS and OS benefit could be due to the differences in patient characteristics in the trials, previous treatments received, the distribution of histology subtypes included in each treatment arm, and the IMDC risk or due to the small sample size in CABOSUN II.

6.16 The significant PFS but non-significant OS benefits were consistent with the outcomes of cabozantinib in the ccRCC setting. The PBAC assessment of cabozantinib versus sunitinib in the ccRCC population noted that "... the difference in OS for cabozantinib versus sunitinib was not statistically significant and appeared to be decreasing with additional follow-up" (paragraph 7.4, Cabozantinib, Public Summary Document (PSD) November 2020 PBAC meeting).

6.17 Table 5 presents the results of objective response rate (ORR) across trials.

**Table 5: Results of ORR across the trials**

Trial	Response	Cabozantinib	Sunitinib	Relative risk (95% CI)	Risk difference (95% CI)
<b>SWOG 1500<sup>a</sup></b>	Overall response	10/44 (22.7%)	2/46 (4.3%)	<b>5.22 (1.21, 22.53)</b>	<b>18.38 (3.29, 33.47)</b>
	Partial response	8/44 (18.2%)	2/46 (4.3%)	NR	NR
	Stable disease	23/44 (52.3%)	23/46 (50.0%)	NR	NR
	Progressive disease	4/44 (9.1%)	11/46 (23.9%)	NR	NR
<b>CABOSUN II<sup>b</sup></b>	Overall response	NR	NR	NR	NR
	Partial response	2/15 (13.3%)	1/17 (5.9%)	2.3 (0.12, 133.7)	7.5 (-13.8, 28.7)
	Stable disease	8/15 (57.1%)	9/17 (52.9%)	NR	NR
	Progressive disease	4/15 (28.6%)	6/17 (35.3%)	NR	NR

Source: Table 2-14, p48, Table 2-15, p49 of the submission; Johns et al. (2023); Pal et al. (2021).

CI = confidence interval; n = number of participants reporting data with events; N = total participants in group; NR, not reported; ORR = objective response rate.

Bold indicates statistically significant results, p-values were one sided.

<sup>a</sup> Cut-off date was 16 October 2020. <sup>b</sup> study was conducted between 9/2018 and 6/2021.

6.18 ORR in SWOG 1500 was defined as the combined rate of confirmed and unconfirmed partial response and confirmed and unconfirmed complete response. ORR in CABOSUN II was defined as the best response recorded from the start of treatment until disease progression/recurrence.

6.19 Overall response was significantly higher in the cabozantinib arm than in the sunitinib arm in SWOG 1500. In CABOSUN II, overall response was not reported.

6.20 The submission used a 'frame of reference' approach to inform pricing of cabozantinib in nccRCC. The frame of reference approach was based on the claim of non-inferior (similar) effectiveness of cabozantinib in nccRCC and ccRCC. Thus, the submission conducted a naïve comparison of the results from SWOG 1500 (nccRCC) with the results from CABOSUN and METEOR (ccRCC).

6.21 For the ccRCC setting, the submission presented evidence from CABOSUN (cabozantinib vs sunitinib) for the first-line therapy, and from METEOR (cabozantinib vs everolimus) for the second -line treatment post-TKI. The ESC noted that the METEOR trial had very limited relevance to the submission as it does not include sunitinib as a comparator and patients had received prior VEGFR-targeted treatment, which is unlikely to be reflective of nccRCC patients treated in Australian clinical practice.

6.22 Table 6 presents key features of ccRCC trials used.

**Table 6: Key features of ccRCC trials**

Trial	N	Design/ duration	Risk of bias	Patient population	IMDC/MSK CC risk	Outcomes
<b>Cabozantinib versus sunitinib</b>						
CABOSUN	157	R, OL 25 months (median duration of follow-up)	High	Previously untreated patients with advanced or metastatic clear cell RCC	IMDC risk: Poor (19%), intermediate (81%)	PFS, OS, ORR, AEs
<b>Cabozantinib versus everolimus</b>						
METEOR	ITT: 658 PITT: 375	R, OL <sup>a</sup> , MC May 2015 database lock: ITT: 5.9 mths PITT <sup>b</sup> : 10.7 mths Dec 2015 database lock: ITT: 13.0 mths	Moderate	Advanced/metastatic RCC following at least one prior VEGFR-targeted treatment, Karnofsky PS of at least 70%	MSKCC risk: Poor (14%), intermediate (43%), favourable (43%)	PFS (primary) <sup>b</sup> OS, ORR, EQ5D

Source: Table 2-20, p55 of the submission. Table 3, p8 of Cabozantinib, PSD, December 2017 PBAC Meeting. Choueiri et al. (2015), supplementary Figure S4.

AEs = adverse events; ccRCC = clear cell renal cell carcinoma; OL= open label; R = randomised; ITT = intention to treat; MC = multi-centre; mths = months; MSKCC = Memorial Sloan Kettering Cancer Center criteria; NR = not reported; ORR = objective response rate; OS = overall survival; PFS = progression free survival; PITT= primary intention to treat; PS = performance status; RCC = renal cell carcinoma; VEGFR = vascular endothelial growth factor receptor.

<sup>a</sup> Tumour response and progression were assessed by a blinded centralised independent review committee.

<sup>b</sup> The primary outcome was PFS in the primary intention to treat (PITT) population, which was defined as the first 375 randomised patients.

6.23 The effectiveness of cabozantinib and sunitinib in nccRCC from SWOG 1500 was naively compared with results obtained from ccRCC patients from CABOSUN. CABOSUN was a head-to-head, Phase II, randomised, open-label trial comparing cabozantinib to sunitinib, in previously untreated patients with advanced or metastatic ccRCC, with IMDC intermediate to poor risk disease (n = 157). METEOR was a head-to-head, open-label trial comparing cabozantinib with everolimus in patients with advanced or metastatic ccRCC who had progressed after prior vascular endothelial growth factor receptor (VEGFR)-targeting TKI therapy (METEOR; N=658).

6.24 The patient populations included in CABOSUN, METEOR, and SWOG 1500 were heterogeneous. Apart from ccRCC (CABOSUN and METEOR) and papillary nccRCC (SWOG 1500), the patients included in CABOSUN were previously untreated with any TKI while patients included in METEOR had at least one prior VEGFR-targeted treatment. Only 7% of SWOG 1500 patients had previous systemic treatment. Furthermore, SWOG 1500 included 26% favourable, 61% intermediate, and 14% poor

IMDC risk patients, while CABOSUN included 81% intermediate and 19% poor IMDC risk patients. However, METEOR included 43% favourable, 43% intermediate, and 14% poor risk patients according to the Memorial Sloan Kettering Cancer Center (MSKCC) criteria. There were more patients with favourable risk in SWOG 1500 compared with CABOSUN, but SWOG 1500 included fewer patients with favourable risk compared to METEOR. In addition, SWOG 1500 enrolled patients with a performance status (PS) of  $\leq 1$  (Zubrod score), and 62% of them had a score of 0, CABOSUN enrolled patients with a PS of  $\leq 2$  (Eastern Cooperative Oncology Group (ECOG)) and 14% of these patients had a PS of 2, while 46% had a PS of 0. The METEOR study enrolled patients with a PS of  $\leq 1$ , with 69% having a score of 0, using the ECOG scale. Overall, CABOSUN had patients with worse PS compared with SWOG 1500, while PS in SWOG 1500 and METEOR was comparable.

- 6.25 Table 7 presents the naïve comparison of PFS and OS results of SWOG 1500 and CABOSUN and METEOR.

Table 7: Naïve comparison of results of PFS and OS from SWOG 1500, CABOSUN, and METEOR

Trial	Cabozantinib		Comparator		Difference in median (months)	p value <sup>a</sup>	HR (95% CI)
	n/N with event (%)	Median months (95% CI)	n/N with event (%)	Median months (95% CI)			
<b>PFS</b>							
SWOG 1500 <sup>b</sup> (cut-off date: October 2020)	32/44 (72.7%)	9.0 (5.6, 12.4)	Sunitinib: 38/46 (82.6%)	Sunitinib: 5.6 (2.9, 6.7)	3.4	0.019	<b>0.6</b> <b>(0.37, 0.97)</b>
CABOSUN <sup>c</sup> (IRC assessed-September 2016 data-cut-off, FDA censoring rules)	43/79 (54.4%)	8.6 (6.8, 14.0)	Sunitinib: 49/78 (62.8%)	Sunitinib: 5.3 (3.0, 8.2)	3.3	0.0008	<b>0.48</b> <b>(0.31, 0.74)</b>
METEOR <sup>d</sup> (cut-off date: May 2015)	121/187 (64.7%)	7.4 (5.6, 9.1)	Everolimus: 126/188 (67.0%)	Everolimus: 3.8 (3.7, 5.4)	3.6	<0.001	<b>0.59</b> <b>(0.46, 0.76)</b>
<b>OS</b>							
SWOG 1500 <sup>b</sup> (cut-off date: October 2020)	22/44 (50.0%)	20.0 (11.3-NR)	Sunitinib: 24/46 (52.2%)	Sunitinib: 16.4 (12.8-21.6)	3.6	NR	0.84 (0.47-1.51)
CABOSUN <sup>c</sup> (cut-off date: July 2017)	43/79 (54.4%)	26.6 (14.6, NE)	47/78 (60.3%)	21.2 (16.3, 27.4)	5.4	0.29	0.80 (0.53,1.21)
METEOR <sup>d</sup> (cut-off date: December 2015)	140/330 (42.4%)	21.4 (18.7, NE)	Everolimus: 180/328 (54.9%)	Everolimus: 16.5 (14.7, 18.8)	4.9 <sup>e</sup>	0.0003	0.67 (0.53, 0.83)

Source: Table 2-21, p55, Table 2-22, p56, Table 2-25, p58, Table 2-26, p58, Table 2-27, p59, Table 3-2, p69, Table 3-4, p71 of submission; Table 4, p9, Table 5, p11 of cabozantinib, PSD, December 2017 PBAC Meeting, Table 5, p10 of cabozantinib, PSD PBAC Meeting November 2020.

CI= confidence interval; HR= hazard ratio; IRC = Independent Radiographical Committee; n = number of participants with event; N = total participants in group; NE = not estimable; NR = not reported; PFS = progression free survival.

<sup>a</sup> Log-rank p-value (stratified)

<sup>b</sup> Only included papillary RCC and patients on first- and second-line therapies.

<sup>c</sup> Included ccRCC patients who were on first-line therapy.

<sup>d</sup> Included ccRCC patients who were on second-line therapies (post-TKI).

<sup>e</sup> calculated for this submission.

Bold indicates significant statistical difference.

- 6.26 The naïve comparison showed that the relative effectiveness of cabozantinib compared to sunitinib appears to be comparable in the first line of treatment across the ccRCC and nccRCC; however, this comparison is affected by the heterogeneity between the trials.
- 6.27 The comparison in the second-line treatment setting is uncertain because there is no common comparator between METEOR and SWOG 1500 (i.e., everolimus and sunitinib). Furthermore, only 5% of cabozantinib patients received prior systemic therapy compared to 100% in METEOR. However, as there are currently no TKIs PBS listed for nccRCC the ESC agreed with the Commentary that it would be expected that the majority of PBS patients would be treated in the first line setting. Therefore, the results for the second line comparison are of less relevance.

**Comparative harms**

6.28 Table 8 presents adverse effects reported in the SWOG 1500 trial.

**Table 8: Summary of key adverse events in SWOG 1500<sup>1</sup>**

Adverse event	Cabozantinib (N=43)		Sunitinib (N=45)		RR (95% CI)
	Any grade n (%)	Grade 3 or 4 n (%)	Any grade n (%)	Grade 3 or 4 n (%)	
<b>Pal et al (2021)<sup>a</sup></b>					
Overall	42/ (98)	32 (74)	42 (93)	31 (69)	NR
Fatigue	30 (70)	6 (14)	26 (58)	3 (7)	NR
Diarrhoea	24 (56)	2 (5)	22 (49)	3 (7)	NR
Nausea	15 (35)	0	19 (42)	4 (9)	NR
Hypertension	28 (65)	14 (33)	16 (36)	8 (18)	NR
Anorexia	19 (44)	1 (2)	14 (31)	0	NR
Mucositis oral	16 (37)	1 (2)	13 (29)	0	NR
Hand-foot syndrome	21 (49)	9 (21)	11 (24)	0	NR
Vomiting	6 (14)	0	11 (24)	1 (2)	NR
Dehydration	1 (2)	0	5 (11)	1 (2)	NR
Abdominal pain	6 (14)	3 (7)	3 (7)	1 (2)	NR
Dyspnoea	5 (12)	0	3 (7)	0	NR
Gastrointestinal disorders not otherwise specified	7 (16)	1 (2)	3 (7)	0	NR
Pain in extremity	6 (14)	1 (2)	3 (7)	0	NR
Rash maculopapular	8 (19)	0	3 (7)	0	NR
Thromboembolic event	8 (19)	5 (12)	1 (2)	0	NR
Platelet count decreased	8 (19)	0	18 (40)	2 (4)	NR
Anaemia	10 (23)	0	15 (33)	6 (13)	NR
White blood cell decreased	9 (21)	0	13 (29)	5 (11)	NR
Neutrophil count decreased	7 (16)	0	11 (24)	4 (9)	NR
Lymphocyte count decreased	6 (14)	0	10 (22)	2 (4)	NR
AST increased	14 (33)	0	8 (18)	1 (2)	NR
Proteinuria	7 (16)	1 (2)	7 (16)	1 (2)	NR
ALT increased	13 (30)	1 (2)	6 (13)	1 (2)	NR
Hypoalbuminaemia	6 (14)	0	6 (13)	1 (2)	NR
Hypophosphataemia	11 (26)	4 (9)	3 (7)	0	NR
Hypocalcaemia	10 (23)	1 (2)	1 (2)	0	NR
Hypomagnesaemia	9 (21)	2 (5)	0	0	NR
<b>From US trial Register<sup>b</sup></b>					
All deaths	22/44 (50)	NR	24/46 (52)	NR	NR
Any AEs (not including Serious AEs)	41/43 (95)	NR	44/45 (98)	NR	NR
Serious AEs	19/43 (44)	NR	15/45 (33)	NR	NR

Source: Table 2-17, p51, and Table 2-18, p52 of the submission.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CI = confidence interval; n = number of participants reporting data; N = total participants in group; NR = not reported, RR = relative risk.

<sup>a</sup> Pal et al (2021) reported adverse events that occurred in at least 10% of patients in the cabozantinib or sunitinib groups. CABOSUN II did not report any adverse events. <sup>b</sup> Posted in US trial Register, 2<sup>nd</sup> September 2022

6.29 Only SWOG 1500 reported adverse events (AEs) for cabozantinib compared with sunitinib. CABOSUN II did not report any AEs in the published abstract or trial registry.

- 6.30 Safety data for SWOG 1500 were available from two publicly available sources, the peer reviewed published results in (Pal et al, 2021) and the results posted to the US clinical trials registry. There were inconsistencies between the published safety data and that posted to the US Registry for the SWOG 1500 study, possibly due to different data cut-offs.
- 6.31 SWOG 1500's safety results showed that 74% of cabozantinib-treated patients and 69% of patients treated with sunitinib experienced at least one grade 3 or 4 AE. Patients treated with cabozantinib experienced grades 3 or 4 hand-foot syndrome (21%) and thromboembolic events (12%), whereas no patients in the sunitinib arm experienced grade 3/4 events for these AEs.
- 6.32 The most common grade 3 or 4 AEs with sunitinib were hypertension (18%), anaemia (13%), and decrease in white blood cell count (11%). The most common grade 3 or 4 adverse events with cabozantinib were hypertension, hand-foot syndrome, and fatigue. One grade 5 adverse event (i.e., death) within 30 days of the last dose of study medication was reported in one patient receiving cabozantinib, secondary to a thromboembolic event.
- 6.33 In the US registry, more patients in the cabozantinib group reported serious AEs (44%) compared to the sunitinib group (33%). Thromboembolic events were the most common SAE in the cabozantinib group (11.63%). Three patients (6.98%) in the cabozantinib group reported a SAE of neoplasm benign, malignant and unspecified.

### ***Benefits/harms***

- 6.34 No benefit/harms table is presented as there are no active comparators PBS listed for nccRCC and evidence presented in the submission was based on a comparison with sunitinib.

### ***Clinical claim***

- 6.35 The submission described cabozantinib as superior in terms of effectiveness in PFS and ORR compared to sunitinib. The ESC agreed with the Commentary that this claim was adequately supported in the papillary RCC population, but uncertain in other subtypes of nccRCC.
- 6.36 The effectiveness of cabozantinib compared to sunitinib in post-TKI remained uncertain since only 5% of cabozantinib patients in SWOG 1500 received prior systemic treatment.
- 6.37 In November 2020, the PBAC considered that the claim of non-inferior (different but broadly comparable) comparative safety versus sunitinib was reasonable in patients with ccRCC (paragraph 7.6, cabozantinib, PSD, November 2020 PBAC Meeting). The ESC noted that, while not statistically significant, cabozantinib showed higher rates of adverse events than sunitinib for many clinically significant events in SWOG 1500 (including fatigue, hypertension, hand-foot syndrome, and elevated liver enzymes). The ESC considered that AEs for cabozantinib are generally manageable with dose

reductions and are not usually clinically limiting. The ESC noted PBAC's previous advice that comparative safety for cabozantinib and sunitinib was "different but broadly comparable" but the ESC considered the claim of comparable safety is uncertain.

- 6.38 The submission also described the effectiveness (in terms of PFS and ORR) of cabozantinib compared to sunitinib in patients with nccRCC as essentially similar to that observed in patients with ccRCC. The relative effectiveness of cabozantinib compared to sunitinib appears to be comparable in the first line of treatment across ccRCC and nccRCC; however, this was based on a naïve comparison and is affected by heterogeneity between the trials. The PSCR noted this is a limitation of the paucity of available evidence within the identified population, and the best evidence available is used as a basis for the submission. The ESC considered that there remained a high level of uncertainty in the effectiveness claim due to the paucity of evidence available.
- 6.39 The comparability of cabozantinib performance across nccRCC and ccRCC in post-TKI treatment is uncertain because there is no common comparator between METEOR and SWOG 1500 (i.e., everolimus and sunitinib) and only 5% of cabozantinib patients received prior systemic therapy. However, the ESC considered the second line comparison was of little relevance for the submission as there are no other TKIs PBS-listed for nccRCC.
- 6.40 The PBAC considered that the claim of superior comparative effectiveness compared with sunitinib was reasonable for PFS and ORR and the claim of non-inferior OS with sunitinib was reasonable. The PBAC also noted the limitations of the evidence in less common RCC subtypes but considered that it was reasonable to conclude, on the basis of the available evidence, that there is comparable efficacy for cabozantinib in nccRCC and ccRCC, particularly in the first line setting.
- 6.41 The PBAC considered that the claim of non-inferior comparative safety was uncertain based on the limited evidence available, however considered that there are unlikely to be differences in comparative safety in patients with nccRCC compared with ccRCC.

### ***Economic analysis***

- 6.42 The submission claimed that conducting a cost-effectiveness analysis was not feasible since the available clinical evidence was not derived from a company sponsored clinical trial, and therefore, a full clinical study report and individual patient data were not available (e.g., duration of treatment and utility data). Additionally, the submission noted that the PBAC had not assessed the cost-effectiveness of sunitinib, the comparator. The ESC noted a modelled cost-effectiveness analysis compared with BSC could have been conducted using published data, such as the survival curves (OS and PFS) from SWOG 1500 for cabozantinib and utility scores and other natural history data from studies in advanced RCC.
- 6.43 The submission considered that conducting a cost-comparison analysis specific to nccRCC, but similar to the analysis utilised to derive the current price for cabozantinib in the first-line treatment of ccRCC in reference to sunitinib, was not feasible because

the duration of treatment data is not available for the nccRCC population. The cost-comparison analysis for ccRCC accepted by the PBAC in November 2020 was based on pre- and post-progression costs of treatment with cabozantinib compared with sunitinib, assuming the same duration of OS. The PBAC previously accepted that the analysis adequately demonstrated that cabozantinib is cost-effective if the cost per day for cabozantinib that is no higher than the average cost per day for sunitinib (paragraph 7.7, cabozantinib, PSD, November 2020 PBAC Meeting). In this comparison patients treated with cabozantinib stayed on treatment for longer than patients on sunitinib (12.6 months for cabozantinib vs 7.2 months for sunitinib). Although this resulted in a higher total estimated drug cost per patient for cabozantinib, this was offset by lower post-progression costs (paragraph 7.9, cabozantinib, PSD, November 2020 PBAC Meeting). The Commentary noted that PFS could have been used to inform duration on treatment for nccRCC, however there was also no information regarding post-progression treatments in the trials for nccRCC.

- 6.44 The submission proposed a ‘frame of reference’ approach to inform a suitable price for cabozantinib in advanced nccRCC. The premise of this approach is:
- Cabozantinib is superior to sunitinib with respect to PFS and ORR, and non-inferior with respect to OS and safety in advanced nccRCC.
  - The effectiveness of cabozantinib in terms of PFS and ORR compared to sunitinib in patients with nccRCC is similar to that observed in ccRCC.

The submission argued, on this basis, it is reasonable to apply the same price of cabozantinib accepted for ccRCC in the November 2020 to nccRCC.

- 6.45 The current pricing of cabozantinib in ccRCC is a weighted price across first-line (i.e., patients untreated by TKIs) and post-TKI patients. The PBAC noted that the prices and weighting as stated in the submission were incorrect. The agreed prices and weighting are as follows:
- The first-line price was established based on a cost-analysis with sunitinib (effective price \$ $\downarrow$ ). The term ‘cost-analysis’ was used instead of cost-minimisation since the analysis relied on the difference in PFS and associated differences in treatment duration and time on post-progression therapy (paragraph 6.19, cabozantinib, PSD, November 2020 PBAC Meeting).
  - The post-TKI price was established based on cost-minimisation with nivolumab (effective price \$ $\downarrow$ ). That cost-minimisation approach was based on the equi-effective doses of cabozantinib 45.15 mg daily and nivolumab 240.6 mg (80.2 kg x 3 mg/kg) every 14 days, assuming equal treatment durations (paragraph 6.49, cabozantinib PSD, December 2017 PBAC Meeting). Nivolumab was recommended by the PBAC following a cost-effectiveness analysis compared to everolimus (paragraph 7.1, cabozantinib PSD, December 2017 PBAC Meeting).
  - The weighted net effective price (\$ $\downarrow$ ) was based on a weighting of 74% first-line and 26% second-line (post-TKI) scripts.

- 6.46 The price using 95% first-line and 5% second-line therapy (as in SWOG 1500) would be \$ $\downarrow$ , which is about 17% lower than the proposed effective price. The PSCR argued that there is no evidence that using a weighted price based on lines of treatment in SWOG 1500 would reflect the actual weighting of use across lines of treatment within nccRCC patients on the PBS and alternative clinical trial report higher rates of previous systemic treatments. The ESC considered that in the nccRCC setting patients would be treated almost exclusively in the first line setting as there are no PBS-listed alternatives, and therefore the first-line price would be more applicable for this population. The pre-PBAC response disagreed with the ESC advice that patients would be treated almost exclusively in the first line setting and stated that < 500/< 500 (27.4%) of patients enrolled in the compassionate access program were not treatment naïve, with the majority of these having accessed clinical trials. The PBAC considered that there may be a small number of patients who receive cabozantinib as second-line treatment in the first year of listing, however the agreed first-line price for ccRCC should apply in the nccRCC setting as it would be expected that, after listing on the PBS, cabozantinib is the preferred first-line treatment for these patients. The PBAC considered that the weighted price for RCC should assume 25% of use in the nccRCC population and 75% in the ccRCC population.
- 6.47 Table 7 (above) provides a naïve comparison of PFS results for trials that included nccRCC (SWOG 1500) and ccRCC (CABOSUN and METEOR) patients, to inform the frame of reference approach. The frame of reference approach has the following limitations:
- The applicability issues related to SWOG 1500, mainly including only patients with papillary RCC.
  - Issues regarding the naïve comparisons of nccRCC and ccRCC trials as outlined above in paragraphs 6.26 and 6.27.
  - In the context of nccRCC, evidence was limited pertaining to the duration of treatment and the associated costs post disease progression. Consequently, the applicability of the cost derived from the duration of treatment and offsets from post-progression treatment costs in ccRCC to nccRCC is uncertain.

### ***Drug cost/patient/month***

- 6.48 The cost per patient per month for cabozantinib was based on the price of cabozantinib in ccRCC patients, i.e., effective dispensed price for maximum quantity (DPMQ) \$ $\downarrow$ .

### ***Estimated PBS usage & financial implications***

- 6.49 This submission was considered by DUSC. The submission did not use an epidemiological or market share approach to estimate PBS and RPBS usage and financial implications. The submission used patient access program requests in 2021-

2023 to estimate the utilisation and financial implications associated with the proposal to include nccRCC the current PBS listing of cabozantinib for RCC.

6.50 Table 9 presents key inputs for financial estimates.

**Table 9: Key inputs for financial estimates**

Data	Value	Source	Commentary on the submission	DUSC comments
Patients accessing treatment through sponsor Access programs	2021: [REDACTED] <sup>1</sup> 2022: [REDACTED] <sup>1</sup> 2023: [REDACTED] <sup>1</sup>	Ipsen Named Patient Unsolicited Requests Enrolments	Data as provided by sponsor.	
<b>Eligible population</b>				
Incident patients	Year 1 (2024): [REDACTED] <sup>1</sup> Year 2: [REDACTED] <sup>1</sup> Year 3: [REDACTED] <sup>1</sup> Year 4: [REDACTED] <sup>1</sup> Year 5: [REDACTED] <sup>1</sup> Year 6: [REDACTED] <sup>1</sup>	Extrapolated from Ipsen Patient Access Program requests	Uncertain. Values were taken from the sponsor's compassionate program with 3.78% growth rate. The submission did not provide information about the tyrosine kinase inhibitor (TKI) use or risk level of the patients.	DUSC considered that the model proposed by the sponsor was not fit for purpose. DUSC noted that patients from the patient access program represent a possible prevalent population as they would be the number of treated patients per year. The pre-PBAC response clarified that as patients are treated for approximately 12 months this approximates the annual incidence.
Grandfathered population	Year 1: [REDACTED] <sup>1</sup> Year 2: [REDACTED] <sup>1</sup> Year 3: [REDACTED] <sup>1</sup> Year 4: [REDACTED] <sup>1</sup> Year 5: [REDACTED] <sup>1</sup> Year 6: [REDACTED] <sup>1</sup>	Ipsen Patient Access Program requests	Based on the number of patients enrolled in the Ipsen Patient Access Program for nccRCC	DUSC considered that grandfathered patients would be included in the prevalent population.
Total patients	Year 1: [REDACTED] <sup>1</sup> Year 2: [REDACTED] <sup>1</sup> Year 3: [REDACTED] <sup>1</sup> Year 4: [REDACTED] <sup>1</sup> Year 5: [REDACTED] <sup>1</sup> Year 6: [REDACTED] <sup>1</sup>	Ipsen Patient Access Program requests	Uncertain. Includes adjustment for additional patients from other sources (10%) and reduction to account for proportion eligible for cabozantinib (87.5%).	
<b>Treatment utilisation</b>				
Duration of treatment	12.6 months	CABOSUN	Uncertain. Estimated based on extrapolation of the time on treatment from CABOSUN for clear cell RCC patients (ccRCC).	DUSC considered duration of treatment to be overestimated as it is extrapolated from ccRCC patients in CABOSUN I. DUSC noted ccRCC patients would respond better to cabozantinib treatment compared to nccRCC patients.
<b>Costs</b>				
Cabozantinib	Published DPMQ -\$9,962.13; Effective DPMQ - \$[REDACTED] (corrected during evaluation)	Proposed price for cabozantinib	The submission incorrectly used AEMP to calculate the financial impact of listing cabozantinib, rather than DPMQ.	DUSC agreed with the commentary.
Patient copayment	PBS services:	PBS: 97.84% RPBS: 2.16%	A weighted average co-payment in each of the	DUSC considered this to be reasonable.

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	<p>General - Ordinary Services: \$30.00</p> <p>General - Safety Net Services: \$7.30</p> <p>Concessional - Ordinary Services: \$7.30</p> <p>Concessional - Free Services: \$0</p>		<p>schedule settings is calculated based on patterns of use of currently reimbursed cabozantinib in clear-cell variant RCC using the standard approach</p>	
MBS costs	\$0	Not included	Uncertain. The submission did not include any MBS costs.	DUSC noted that cabozantinib use was likely to result in MBS costs (clinics, blood tests etc). The PBAC considered that there is unlikely to be an increase in MBS costs associated with listing of cabozantinib.

Source: Table 4-2, p74, Table 4-3, p74 of the submission); Section 4 Workbook, 2e Scripts – market; ccRCC = clear cell renal cell carcinoma, AIHW = Australian Institute of Health and Welfare, DPMQ = dispensed price for the maximum quantity, MBS = Medicare Benefits Schedule; nccRCC = non clear cell renal cell carcinoma; NR = not reported; PBAC = Pharmaceutical Benefits Advisory Committee; TKI = tyrosine kinase inhibitor.

*Italics* calculated during the evaluation using the proposed effective AEMP of \$█ and dispensing fees based on pharmacy mark-ups.

The redacted values correspond to the following ranges:

<sup>1</sup> < 500

- 6.51 DUSC noted the sponsor’s current compassionate program is just one treatment option for patients, is not widely advertised and requires case-by-case approval. DUSC considered that using these patient numbers to form the basis of the model assumes all patients have access to the program, which may not be reasonable. The pre-PBAC response noted that the access program has been running since 2018 and is well known to clinicians due to the absence of other treatment options for patients with nccRCC.
- 6.52 DUSC noted that the number of patients from the patient access program represent a possible prevalent population. However, it was unclear whether these patient numbers are reasonable basis for predicting incident patients in the forward years. The pre-PBAC response clarified that as patients are treated for approximately 12 months the number of prevalent patients approximates the annual incidence. The PBAC considered that the estimates of patient numbers appear reasonable. DUSC considered that grandfathered patients would be included in the prevalent population. The PBAC considered that it would be reasonable to include grandfather patients from the access program, however these patients should not have the full treatment duration applied in year 1 of the estimates as they would have initiated non-PBS subsidised treatment in the prior year. The submission assumed that an additional 10% of patients may be treated under the PBS listing from sources not currently captured by the compassionate access program (e.g., post-clinical trials). However, this assumption was uncertain and no further information was available to

confirm this figure. The PBAC considered this estimate of additional patients was uncertain but appeared reasonable.

- 6.53 The submission applied the proportion eligible following the PBS criteria (i.e., poor or intermediate risk; 87.5%) to the patient numbers from the access program. This was based on 12.5% of RCC patients in Australia having favourable risk according to the IMDC risk criteria. This proportion was obtained from the RCC population in Australia, however it was uncertain whether this would apply to nccRCC patients.
- 6.54 DUSC considered that an epidemiological approach may produce a more accurate estimate of incident patients. DUSC considered that adjustments could be made to the approach in the March 2020 submission for cabozantinib, adapted to nccRCC. This approach estimated < 500 eligible patients in the first year of listing (3,617 incident kidney cancer cases, 90% RCC, 20% nccRCC, 30% Stage IV diagnosis). The PBAC considered that there was some uncertainty in the approach to estimating patient numbers, however considered that revision of the approach was not necessary as the uncertainty would be managed through incorporation of expenditure for nccRCC patients into the existing RSA financial caps for ccRCC.
- 6.55 DUSC considered a 100% uptake rate is likely overestimated. DUSC noted some patients may seek alternative treatments, such as clinical trials, and noted a proportion of patients may not seek treatment given limited benefit in some histologies. The Pre-PBAC response noted that as patient estimates were based on the access program (rather than the total eligible population), the assumption of 100% uptake was reasonable. The PBAC agreed with the sponsor that this approach was reasonable given the basis for the estimated patient numbers.
- 6.56 DUSC considered the duration of treatment to be overestimated as it is based on the extrapolated treatment duration for ccRCC patients in CABOSUN. DUSC noted ccRCC patients are likely to respond better to cabozantinib treatment compared to nccRCC patients and that the treatment duration in nccRCC patients would likely be shorter. The PBAC noted that the median PFS for nccRCC from SWOG 1500 (9 months) was slightly longer than that for ccRCC from CABOSUN (8.6 months) and considered that the extrapolated treatment duration from CABOSUN is likely to be comparable to that in nccRCC patients.
- 6.57 Table 10 presents the estimated use and financial implications of cabozantinib between 2024 and 2029 for the PBS/RPBS.

**Table 10: Estimated use and financial implications using the effective DPMQ of cabozantinib.**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated extent of use</b>						
Number of patient years of treatment <sup>a</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>
Number of scripts dispensed <sup>b</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>
<b>Estimated financial implications of cabozantinib</b>						
Cost to PBS/RPBS less copayments <sup>b</sup>	\$█ <sup>3</sup>	\$█ <sup>3</sup>	\$█ <sup>3</sup>	\$█ <sup>3</sup>	\$█ <sup>3</sup>	\$█ <sup>3</sup>
<b>Estimated financial implications for other medicines (cost offsets)</b>						
Cost to PBS/RPBS less copayments	\$0	\$0	\$0	\$0	\$0	\$0
<b>Net financial implications</b>						
Net cost to PBS/RPBS	\$█ <sup>3</sup>	\$█ <sup>3</sup>	\$█ <sup>3</sup>	\$█ <sup>3</sup>	\$█ <sup>3</sup>	\$█ <sup>3</sup>

Source: Section 4 Workbook of submission.

GF = grandfathered; mon. = months; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriated Pharmaceutical Benefits Scheme.

<sup>a</sup> Assumes 12.6 months of treatment per incident patient and 6 months for prevalent (grandfather) patients.

<sup>b</sup> scripts and costs corrected during evaluation by using correct duration of treatment groups for the number of scripts and using the effective DPMQ of \$█ for cabozantinib.

The redacted values correspond to the following ranges:

<sup>1</sup> < 500

<sup>2</sup> 500 to < 5,000

<sup>3</sup> \$0 to < \$10 million

- 6.58 There were a number of errors in the financial estimates worksheet provided in the submission. After these were corrected the total cost to the PBS/RPBS of listing cabozantinib was estimated to be \$0 to < \$10 million in Year 6, and a total of \$10 million to < \$20 million in the first 6 years of listing.
- 6.59 Overall, DUSC considered the estimates presented in the submission to be underestimated due to potential underestimation of the total number of eligible patients. The PBAC considered the financial estimates to be reasonable although noted that there was some remaining uncertainty, however this uncertainty was mitigated by the proposed inclusion of nccRCC within the existing ccRCC RSA caps.

### **Financial Management – Risk Sharing Arrangements**

- 6.60 A Deed of Agreement exists between the sponsor and the Commonwealth for the listing of cabozantinib on the PBS in RCC. As noted above, the submission proposed that the incremental expenditure associated with this nccRCC submission be incorporated within the existing Deed of Agreement and Risk Sharing Arrangement (RSA) caps, with █% rebate for expenditure above the financial caps.
- 6.61 In the first year of the introduction of cabozantinib for ccRCC patients (year 1), the expenditure reached █% of the cap amount, followed by █% in 2020-2021 (year 2). The ccRCC expenditure in 2022-2023 was \$█ which was about █% of the RSA cap in that year (\$█). For 2024-2025 (year 4) and 2025-2026 (year 5) RSA caps are \$█ and \$█, respectively. The pre-PBAC response estimated that an additional < 500 patients (approximately) could be treated in the 2024-2025 period without the financial caps being exceeded, and that the risk of utilisation beyond this would be borne by the sponsor due to the █% rebate for use exceeding the caps.

For more detail on PBAC's view, see section 7 PBAC outcome.

## **7 PBAC Outcome**

- 7.1 The PBAC recommended the renal cell carcinoma (RCC) restriction for cabozantinib be extended to include the treatment of non-clear cell renal cell carcinoma (nccRCC). The PBAC considered that there is a high clinical need for effective treatments in the small subset of RCC patients with nccRCC as there are currently no targeted treatments available on the PBS. The PBAC noted that the evidence is limited but considered that the clinical benefit in patients with nccRCC appears to be similar to that in patients with clear cell RCC (ccRCC), particularly in the first line setting. The PBAC considered that on this basis it was reasonable to accept that cabozantinib would be cost-effective for treatment of nccRCC at the same first-line price as accepted for ccRCC, but with revised weighting of the prices to reflect differences in the treatment algorithm.
- 7.2 The PBAC was satisfied that cabozantinib provides, for some patients, a significant improvement in efficacy over sunitinib or over best supportive care (no drug therapy).
- 7.3 The PBAC noted advice from clinicians and organisations via the sponsor hearing and consumer comments that there is a high unmet need for treatments for patients with nccRCC. Although patients with ccRCC have several treatment options, for the small number of patients with nccRCC, there are no targeted treatments available on the PBS, only the Ipsen cabozantinib access program and clinical trials. The consumer comments noted that compassionate access programs and access to trials are not guaranteed, not available to all patients, and many patients progress while awaiting approval.
- 7.4 The submission requested to remove 'clear cell variant' from the current PBS indication to broaden the listing to include all RCC clear cell and non-clear cell subtypes. No other changes to the RCC initial and continuing restrictions for cabozantinib were proposed. The PBAC considered that the proposed change to the indication, which maintained the same circumstances of use across all advanced RCC, was reasonable. The PBAC noted that there are limited clinical data available in nccRCC subtypes other than papillary, which are relatively rare and affect only a small number of patients, however further data are not likely to become available. The PBAC also noted that cabozantinib would be the preferred first line therapy for patients with nccRCC, but considered that it would be reasonable for the listing to include patients whose disease has progressed despite treatment with a prior TKI, consistent with the existing restrictions for ccRCC. The PBAC considered that the proposed grandfather restriction was reasonable, to allow transition from non-PBS to PBS-subsidised supply for patients with stable or responding disease.
- 7.5 The PBAC noted that the submission presented sunitinib as primary comparator because it is among the treatment options for nccRCC patients recommended by the NCCN clinical practice guidelines, though it is not PBS listed in this indication. The PBAC noted that relevant comparators also include other TKIs, immunotherapy,

immunotherapy in combination with a TKI, or no drug treatment. However, the PBAC considered that the most appropriate comparator was best supportive care, noting that no treatments are listed on the PBS for nccRCC. The PBAC noted the comparison of cabozantinib versus sunitinib was presented in the submission to support the claim that the benefit of cabozantinib in nccRCC is similar to the benefit previously assessed for cabozantinib versus sunitinib in ccRCC.

- 7.6 The PBAC noted the submission was based on two head-to-head prospective RCTs comparing cabozantinib and sunitinib for the treatment of advanced nccRCC (SWOG 1500 and CABOSUN II). The PBAC noted that SWOG 1500 included patients with papillary RCC only, which limits the generalisability of its results to other nccRCC subtypes. In addition, few patients in SWOG 1500 (7% overall) had received prior systemic therapy, however the PBAC considered that cabozantinib would be expected to be the preferred first line therapy, therefore this may be reasonably representative of the PBS population. The PBAC noted that the CABOSUN II trial included all nccRCC subtypes but was terminated early and as a result had few patients (N=22) and a high level of bias due to imbalances across the treatment arms in the nccRCC subtypes. The PBAC considered that the claim of superior PFS and ORR, and non-inferior OS of cabozantinib compared with sunitinib in advanced papillary RCC was adequately supported by the data. The PBAC noted that the efficacy of cabozantinib in other subtypes was unclear as data are limited, however cabozantinib does appear to be active in other nccRCC subtypes and due to the rarity of these subtypes more data are unlikely to become available.
- 7.7 The submission used a ‘frame of reference’ approach to inform pricing of cabozantinib in nccRCC, based on the claim or similar relative effectiveness of cabozantinib in nccRCC and ccRCC. Therefore, the submission conducted a naïve comparison of the results from SWOG 1500 (in nccRCC) with the results from two RCTs comparing cabozantinib and sunitinib (CABOSUN) and everolimus (METEOR) for treatment of advanced ccRCC. The PBAC considered that the METEOR trial was not relevant as it was in patients with prior VEGFi therapy and the comparator (everolimus) differed from the trials in nccRCC. The PBAC considered that the naïve comparison had a high level of uncertainty as it was based on limited data, with potential heterogeneity between the trial populations in addition to the difference in RCC subtype. However, the PBAC acknowledged that there is unlikely to be additional data and considered that it was reasonable to conclude, on the basis of the available evidence, that there is comparable efficacy for cabozantinib in nccRCC and ccRCC, particularly in the first line setting, which is the most relevant for the PBS population.
- 7.8 The PBAC recalled that it had previously considered that the claim of non-inferior (different but broadly comparable) comparative safety versus sunitinib was reasonable in patients with ccRCC (paragraph 7.6, cabozantinib, PSD, November 2020 PBAC Meeting). The PBAC noted that cabozantinib showed higher rates of adverse events than sunitinib for many clinically significant events in SWOG 1500 (including fatigue, hypertension, hand-foot syndrome, and elevated liver enzymes). The PBAC

considered the claim of comparable safety for cabozantinib and sunitinib is uncertain but considered that there are unlikely to be differences in comparative safety in patients with nccRCC compared with ccRCC.

- 7.9 The submission did not present an economic evaluation, arguing that it was not feasible due to the lack of data to inform the duration of treatment, post progression costs and utility values in nccRCC, and because the PBAC had not assessed the cost-effectiveness of sunitinib, the comparator in the available clinical evidence. Instead, the submission utilised a ‘frame of reference’ approach whereby the price of cabozantinib accepted by the PBAC at its November 2020 meeting in the ccRCC setting is applied to the nccRCC setting, based on the conclusion that the clinical effectiveness of cabozantinib observed in the two settings is similar. The PBAC noted the ESC advice that although a modelled cost-effectiveness analysis compared with best supportive care could have been conducted using published data, the reliability of any economic model would be limited due to the limited data available. The PBAC noted that the clinical context for nccRCC (where there are no treatments PBS listed) differs to that for ccRCC at the time when cabozantinib was assessed as there were a range of PBS listed treatment options. The PBAC noted this complicates the ‘frame of reference’ approach, however, considered that an alternative approach with a modelled analysis was unlikely to be more reliable. On balance, the PBAC considered that it was reasonable to accept that cabozantinib would be cost-effective for treatment of nccRCC at the same price as accepted for ccRCC. The PBAC advised that acceptance of this approach to demonstrating cost-effectiveness was in the context of a rare subtype with limited clinical data, a small, well-defined population and relatively low financial impact.
- 7.10 The PBAC noted that the current cabozantinib effective price (\$██████) in ccRCC is a weighted price across first-line (74%; \$|) and post-TKI price (26%; \$|). The PBAC considered that there may be a small number of patients who receive cabozantinib as second-line treatment in the first year of listing, however the agreed first-line price for ccRCC should apply in the nccRCC setting as cabozantinib would be the only PBS-listed treatment in this indication and is therefore likely to become the preferred first-line treatment for those patients. However, the PBAC noted that the proposed restrictions allow second-line use following progression on a TKI and considered that it would be reasonable to maintain the restriction wording across nccRCC and ccRCC. The PBAC considered that the weighted price for RCC should assume 25% of use in the nccRCC population and 75% in the ccRCC population.
- 7.11 The PBAC noted that the submission used patient access program requests in 2021-2023 to estimate the utilisation and financial implications associated with a listing including nccRCC. The PBAC considered that it would be reasonable to include grandfather patients from the access program in year 1 of the estimates, however these patients should not have the full treatment duration of 12.6 months applied. The PBAC considered that, after correction of errors in the financial estimates

worksheet and reduction of the treatment duration for grandfather patients, the assumptions and overall financial estimates appeared reasonable.

- 7.1 The PBAC noted a Deed of Agreement exists between the sponsor and the Commonwealth for cabozantinib in ccRCC with 10% rebate for expenditure above agreed RSA financial caps. The submission proposed that the incremental expenditure associated with treatment of nccRCC be incorporated within the existing Deed of Agreement RSA caps. The PBAC considered that there was some uncertainty in the approach to estimating patient numbers, and the cost-effectiveness of cabozantinib in nccRCC, but considered this uncertainty would be adequately managed through incorporation of expenditure for nccRCC patients into the existing RSA financial caps for ccRCC with no increase.
- 7.2 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met. Specifically, the PBAC found that in the circumstances of its recommendation for cabozantinib:
- a) The treatment is not expected to provide a substantial and clinically relevant improvement in efficacy over alternative therapies, as the treatment benefit in nccRCC is unclear, especially with respect to overall survival gain;
  - b) The treatment is expected to address a high and urgent unmet clinical need as there are currently no PBS-listed alternative treatments for nccRCC;
  - c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.
- 7.3 The PBAC noted that this submission is not eligible for an Independent Review as it is a positive recommendation.

**Outcome:**

Recommended

## 8 Recommended listing

- 8.1 Amend existing listing as follows:

Initial treatment (11371L, 11369J, 11360X) and continuing treatment (11374P, 11368H, 11367G)

<b>PBS Indication:</b>	Stage IV clear cell variant renal cell carcinoma (RCC)
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8.2 Add new restriction to allow grandfathering patients as follows:

Name, Restriction, Manner of administration and form	PBS item code	Max. Qty packs	Max Qty units	N° of Rpts	Proprietary Name and Manufacturer
CABOZANTINIB					
Cabozantinib 20 mg tablet, 30	11374P	1	30	5	Cabometyx® Ipsen Pty Ltd
Cabozantinib 40 mg tablet, 30	11368H	1	30	5	Cabometyx® Ipsen Pty Ltd
Cabozantinib 60 mg tablet, 30	11367G	1	30	5	Cabometyx® Ipsen Pty Ltd
<b>Concept ID</b> (for internal Dept. use)	<b>Category / Program:</b> General Schedule/Section 85				
	<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners				
	<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (STREAMLINED)				
	<b>Severity:</b> Stage IV				
	<b>Condition:</b> renal cell carcinoma				
	<b>Indication:</b> Stage IV renal cell carcinoma (RCC)				
	<p><b>Treatment phase:</b> Transitioning from non-PBS to PBS-subsidised supply - Grandfather arrangements for maintenance treatment</p> <p><b>Treatment Criteria:</b> Patient must have previously received non-PBS-subsidised treatment with this drug for this condition prior to [insert date of listing]</p> <p><b>Clinical criteria:</b></p>				
	<p>Patient must have had a prognostic International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) survival risk classification score at treatment initiation with this drug of either: (i) 1 to 2 (intermediate risk), (ii) 3 to 6 (poor risk); document the IMDC risk classification score in the patient's medical records if not already documented,</p> <p>AND</p> <p>Patient must have stable or responding disease according to the Response Evaluation Criteria In Solid Tumours (RECIST)</p>				
	<p>AND</p> <p>The treatment must be the sole PBS-subsidised therapy for this condition.</p>				
	<p>AND</p> <p>Patient must not receive PBS-subsidised treatment with this drug if progressive disease develops while on this drug.</p> <p><b>Administrative Advice:</b> Patients may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a 'Grandfathered' patient must qualify under the 'Maintenance treatment' criteria. This grandfather restriction will cease to operate from 12 months after [insert date of listing]</p>				
	<p><b>Administrative advice:</b> No increase in the maximum number of repeats may be authorised.</p> <p><b>Administrative advice:</b> Special Pricing Arrangements apply.</p>				
	<p><b>Admin advice:</b> Response Evaluation Criteria In Solid Tumours (RECIST) is defined as follows: Complete response (CR) is disappearance of all target lesions. Partial response (PR) is a 30% decrease in the sum of the longest diameter of target lesions. Progressive disease (PD) is a 20% increase in the sum of the longest diameter of target lesions. Stable disease (SD) is small changes that do not meet above criteria.</p> <p><b>Admin advice:</b> A prognostic International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) survival risk score can be calculated here: <a href="https://www.mdcalc.com/imdc-international-metastatic-rcc-database-consortium-risk-model-metastatic-renal-cell-carcinoma">https://www.mdcalc.com/imdc-international-metastatic-rcc-database-consortium-risk-model-metastatic-renal-cell-carcinoma</a>.</p> <p>One point is assigned for each of:</p> <ul style="list-style-type: none"> <li>(i) a time of diagnosis to systemic therapy of less than 1 year</li> <li>(ii) a Karnofsky Performance Status of less than 80%</li> <li>(iii) a haemoglobin less than the lower limit of normal</li> <li>(iv) a corrected calcium level greater than the upper limit of normal</li> <li>(v) a neutrophil count greater than the upper limit of normal</li> <li>(vi) a platelet count greater than the upper limit of normal</li> </ul>				

	<p>Stated normal reference ranges may vary depending on the laboratory providing the measurement. 'Normal' here refers to the individual laboratory's stated normal reference range.</p> <p>Favourable IMDC risk is a score of 0.</p> <p>Intermediate IMDC risk is a score of 1 to 2.</p> <p>Poor IMDC risk is a score of 3 to 6.</p> <p>Document any IMDC risk score assessment in the patient's medical records.</p>
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***This restriction may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.***

## **9 Context for Decision**

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

## **10 Sponsor's Comment**

The sponsor had no comment.